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ESSENTIAL FATTY ACIDS IN PREVENTION OF CARDIOVASCULAR DISEASE EVENTS [ACIDI GRASSI ESSENZIALI NELLA PREVENZIONE DI EVENTI CARDIOVASCOLARI]

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SPECIFICATION /2*

The object of this invention is the use of a pharmaceutical composition containing ethyl esters of essential fatty acids derived from fish oil, in particular as a mixture with a high concentration of eicosapentaenoic acid (EPA) (20:5ω 3) or docosapentaenoic acid (DHA) (22:6ω 3) ethyl esters in prevention of mortality in patients who are in the hospital recovering from acute myocardial infarction (AMI).

It is known that certain essential fatty acids containing fish oil have a therapeutic effect in prevention or healing of cardiovascular disease, for example in treatment of thrombosis, high cholesterol, arteriosclerosis, strokes and hyperlipemia.

By way of example we can cite U.S. patents 5502077, US 5656667 and US 5698594.

From the prior art cited above it is evident that fatty acids of the omega-3 family, more precisely eicosapentaenoic acid (EPA) (20:5ω 3) or docosapentaenoic acid (DHA) (22:6ω 3) are of particular usefulness in healing the cardiovascular conditions mentioned above.

In fact, EPA, as a precursor of PGI2 and TxA3, acts to prevent /3 platelet aggregation and has an antithrombotic effect which can be traced back to an inhibition of the cyclooxygenase enzyme (effect similar to that of aspirin) and/or to competition with arachidonic acid for this enzyme, with consequent decrease in synthesis of PGE2 and TxA2, which are known platelet antiaggregants.

DHA, on the other hand, is the most important component of brain lipids in humans and moreover, since it is a structural component of the platelet cell, intervenes directly to increase the fluidity of the

* Numbers in the margin indicate pagination in the foreign text.

platelets by playing a major role in the antithrombotic action.

International patent application WO89/11521, the description of which is included as a reference, describes in particular an industrial process for extracting animal and/or vegetable oils from mixtures with a high content of polyunsaturated acids, including EPA and DHA, and their ethyl esters.

Mixtures of fatty acids, in particular EPA/DHA, obtained in accordance with WO89/11521, have been observed to be especially useful in treating cardiovascular pathologies.

The treatments currently used in clinical practice have turned out to be insufficient, however, in preventing cardiovascular disease events in general, more specifically mortality, which has been observed in patients who have suffered infarctions, as the result of relapses which occur after an initial episode of acute myocardial infarction.

So there is still a need for a particular and efficacious drug /4 which will prevent these relapses.

The object of this invention is therefore use of essential fatty acids with a high content of EPA-ethyl ester or DHA-ethyl ester or a mixture thereof in preparation of a pharmaceutical composition useful in the prevention of mortality, for example for other cardiovascular events or unforeseen death in patients who have suffered a myocardial infarction.

For purposes of ease of description, "EPA-ethyl ester" and "DHA-ethyl ester" will be referred to hereafter as simply "EPA" and "DHA". An essential fatty acid with a high content of EPA ethyl ester or DHA ethyl ester, in accordance with this invention, will preferably have a content of this ester greater than 30% by weight, in particular from 60

to 100% by weight. These compounds can be obtained with methods already known to those skilled in the art.

When the mixture of essential fatty acids according to this invention contains EPA + DHA, it will preferably have an EPA + DHA content greater than 25% by weight and in particular from around 30 to 100% by weight, preferably around 85% by weight.

In the EPA/DHA mixture, there should preferably be a percentage of EPA of around 40 to 60% by weight and of DHA of around 25 to 45% by weight.

In any case, the most preferable radio between EPA/DHA is around 0.9/1.5.

The object of this invention therefore is a method for preventing mortality in patients who have survived a myocardial infarction, by administering to this patient a pharmaceutical composition containing /5 a therapeutically efficacious quantity of an essential fatty acid with a high content of EPA-ethyl ester or DHA-ethyl ester or a mixture thereof.

PHARMACOLOGY

The efficacy of the treatment according to the invention is, for example, proven by the fact that with this treatment an amazing and very considerable reduction in post-infarction mortality was observed in a clinical study which was carried out over a period of 3.5 years with protocols structured as follows:

1. one "control" group received the normal treatment which infarction patients are conventionally given in clinical practice.
2. one "treated" group, in addition to the therapy the "control" group was receiving, received EPA+DHA 85% (1 g per day).

3. one "treated" group, in addition to the therapy the "control" group was receiving, received vitamin E; and

4. one "treated" group, in addition to the therapy the "control" group was receiving, received vitamin E and EPA+DHA 85% (1 g per day).

What happened was that the group of patients "treated" with protocol 2 above [group 2] compared with "control" group 1 had 20% fewer total mortalities, 40% fewer unforeseen deaths and considerably fewer mortalities caused by other cardiovascular events.

On the other hand, group 3 had results not much different from control group 1. Group 4 had 19% fewer total mortalities compared /6 to the controls with results similar to those obtained for treated group 2.

With regard to the use of a pharmaceutical composition as claimed in this invention, it is of certain utility in clinical therapy in prevention of mortality in patients who have suffered a myocardial infarction.

Based on clinical results obtained, according to a preferred embodiment of the invention, the dose of EPA+DHA mixture having a titer of 85% to be administered to a patient can vary from around 0.7 g to around 1.5 g per day, preferably around 1 g per day.

This amount of product (or amount of only EPA ethyl ester or only DHA ethyl ester) can be administered in the form of more daily doses or preferably in a single dose, in order to obtain the desired blood level. Obviously it is at the clinician's discretion what amount of product to use, based on the patient's condition, age and weight.

Pharmaceutical preparations according to this invention can be prepared using methods known to those skilled in the art. One preferred

manner of administration is orally, leaving it to the discretion of the treating physician, however, whether other means of administration could be used, for example parenteral.

The following examples of formulation are given here by way of illustration without intent to restrict in any way the scope of the invention.

Gelatin capsule /7

Using methods known to those skilled in the pharmaceutical art, capsules having the following composition and containing 1 g of active principle (EPA + DHA in a titer of 85%) per capsule can be thereby prepared:

Formulation 1

EPA ethyl ester	525 mg/capsule
DHA ethyl ester	315 mg/capsule
d-alpha tocopherol	4 IU/capsule
gelatin	246 mg/capsule
glycerol	118 mg/capsule
red iron oxide	2.27 mg/capsule
yellow iron oxide	1.27 mg/capsule

Formulation 2

Ethyl esters of polyunsaturated fatty acids with content of ethyl esters of polyunsaturated omega-3 acids per the following:	1000 mg
eicosapentaenoic acid EPA,	
docosapentaenoic acid DHA)	850 mg
d,1-alpha-tocopherol	0.3 mg

gelatin succinate	233 mg
glycerol	67 mg
sodium p-oxybenzoate	1.09 mg
propyl sodium p-oxybenzoate	0.54 mg

CLAIMS /8

1. Use of essential fatty acids with a high content of eicosapentaenoic acid (EPA) or docosapentaenoic acid ethyl ester (DHA) or a mixture thereof in preparation of a pharmaceutical composition which can be used to prevent mortality in patients who have suffered a myocardial infarction.

2. Use as claimed in Claim 1 wherein the content of EPA + DHA in this mixture is greater than 25% by weight.

3. Use as claimed in Claim 2 wherein the content of EPA + DHA is between approximately 30% and approximately 100% by weight inclusive.

4. Use as claimed in Claim 2 wherein the content of EPA + DHA is approximately 85% by weight.

5. Use as claimed in any of the preceding claims, wherein in the EPA + DHA mixture, EPA is present in an amount of between 40% and 60% by weight.

6. Use as claimed in Claims 1 to 4, wherein in the EPA + DHA mixture, EPA is present in an amount of between 25% and 45% by weight.

7. Use as claimed in any of the preceding claims, wherein the ratio of EPA to DHA is around 0.9/1.5.

8. Use of essential fatty acids with a high content of eicosapentaenoic acid ethyl ester (EPA) in preparation of a pharmaceutical composition which can be used to prevent mortality in patients who have suffered a myocardial infarction.

9. Use of essential fatty acids with a high content of docosapentaenoic acid ethyl ester (DHA) in preparation of a pharmaceutical composition which can be used to prevent mortality in patients who have suffered a myocardial infarction. /9

10. Use as claimed in Claim 8 wherein the content of eicosapentaenoic acid ethyl ester (EPA) is present in an amount greater than 25% by weight.

11. Use as claimed in Claim 10 wherein the content of eicosapentaenoic acid ethyl ester (EPA) is present in an amount between roughly 60 and 100%.

12. Use as claimed in Claim 9 wherein the content of docosapentaenoic acid ethyl ester (DHA) is present in an amount greater than 25% by weight.

13. Use as claimed in Claim 12 wherein the content of docosapentaenoic acid ethyl ester (DHA) is present in an amount between roughly 60 and 100%.